A One-Time Treatment of Lonvoguran Ziclumeran Improves Quality of Life in Patients With Hereditary Angioedema

William R. Lumry,[1] Danny M. Cohn,[2] Emel Aygören-Pürsün,[3] Timothy J. Craig,[4,5] Henriette Farkas,[6] David Maag,[7] Adele Golden,[7] Shruti Nambiar,[7] Brandon Foster,[8] Aleena Banerji[9]

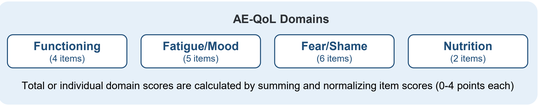
[1]Allergy and Asthma Research Associates Research Center, Dallas, Texas; [2]Amsterdam Cardiovascular Sciences, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [3]University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany; [4]Penn State Health Allergy, Asthma, and Immunology, Hershey, PA; [5]Vinmec Times City and VinUniversity, Hanoi, Vietnam; [6]Hungarian Angioedema Center of Reference and Excellence, Semmelweis University, Budapest, Hungary; [7]Intellia Therapeutics, Cambridge, MA; [8]Psychometrics & Statistics, Lumanity, Morristown, NJ; [9]Massachusetts General Hospital, Boston, MA, and Harvard Medical School, Boston, MA

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Introduction

- Lonvoguran ziclumeran (lonvo-z) is an investigational, *in vivo* CRISPR-based one-time treatment designed to treat hereditary angioedema due to C1 inhibitor deficiency or dysfunction (HAE-C1INH)[1,2]
- In the Phase 3 HAELO study (NCT06634420), lonvo-z 50 mg led to an 87% reduction in attack rate compared with placebo and improved Angioedema Quality of Life Questionnaire (AE-QoL) total score[3]
  - AE-QoL is a validated, 17-item, angioedema-specific patient-reported outcome with a recall period of 4 weeks (**Figure 1**)
  - Higher AE-QoL scores indicate greater quality of life impairment
- Lonvo-z had a favorable safety and tolerability profile in the HAELO study. The most common adverse event in the lonvo-z arm was infusion-related reaction (62%); no serious or Grade ≥3 adverse events were observed[3]

Figure 1. Domains of the AE-QoL



AE-QoL, Angioedema Quality of Life Questionnaire.

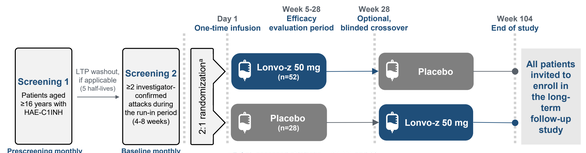
Objective

- Assess the changes and clinical meaningfulness of improvements in quality of life measured by the AE-QoL in patients with HAE-C1INH treated with lonvo-z in the Phase 3 HAELO study

Methods

- The Phase 3 HAELO study is designed to evaluate the efficacy and safety of lonvo-z in patients with HAE-C1INH (**Figure 2**)

Figure 2. HAELO study design



Primary Endpoint
- Time-normalized number of investigator-confirmed HAE attacks from Week 5 through 28

Key Secondary Endpoints[b]
- Number of HAE attacks requiring on-demand treatment (Week 5-28)
- Number of moderate or severe HAE attacks (Week 5-28)
- HAE attack-free status (Week 5-28)
- **Change from baseline to Week 28 in AE-QoL total score**

[a]Patients were stratified by baseline number of investigator-confirmed HAE attacks per month from Screening-2 visit to randomization (>3 vs ≤3). [b]Attacks were investigator confirmed; attack rate was time normalized.
AE-QoL, Angioedema Quality of Life Questionnaire; C1INH, C1 inhibitor; HAE, hereditary angioedema; LTP, long-term prophylaxis.

- Change from baseline at Week 28 in AE-QoL total score was assessed using a mixed model for repeated measures
  - An improvement of AE-QoL total score of ≥6 points was considered to be clinically meaningful and has been previously established as the minimal clinically important difference (MCID)[4]
- To further explore the clinical meaningfulness of these results, the meaningful score difference (MSD) in AE-QoL total score was estimated using an anchor-based approach with the Patient Global Impression of Frequency - Quality of Life (PGI-F-QoL) tool
  - PGI-F-QoL was used as an external anchor to the AE-QoL to help interpret meaningful within-patient change and confirm the appropriateness of the established MCID in the HAELO patient population, consistent with FDA-recommended anchor-based approaches for patient-reported outcomes[5]
  - Additional details on PGI-F-QoL methods and exploratory analyses are included in the **Supplementary Methods**, available by scanning the provided QR code

Results: AE-QoL total score at baseline was consistent between both treatment groups

- As of February 10, 2026, the median follow-up was 7.5 months (range: 4.9-12.8 months)
  - All patients continue to be followed in the study; no patient has discontinued

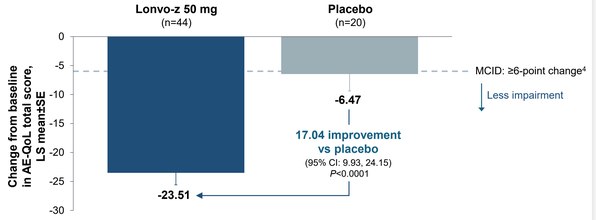
Table 1. HAELO demographics and baseline characteristics

Characteristics[a]	Lonvo-z (n=52)	Placebo (n=28)
Age, median (range), years	42 (23-71)	40 (19-76)
Female, n (%)	35 (67)	20 (71)
Hereditary angioedema type 1, n (%)	49 (94)	25 (89)
Long-term prophylaxis prior to study enrollment, n (%)[b]	35 (67)	22 (79)
Mean monthly attack rate in the 3 months prior to screening (SD)	1.8 (2.1)	1.5 (1.7)
Mean monthly attack rate during run-in period (baseline), mean (SD)[c]	3.5 (1.8)	3.5 (1.9)
AE-QoL total score at baseline, mean (SD)	58.4 (18)	58.0 (13)

[a]Percentages may not sum to 100 due to rounding. [b]Long-term prophylaxis prior to study enrollment was defined as the last dose of long-term prophylaxis being discontinued within 100 days of the Screening-1 visit. [c]Run-in period is from Screening-2 visit to randomization.
AE-QoL, Angioedema Quality of Life Questionnaire.

Change in AE-QoL total score in the lonvo-z arm exceeded the MCID

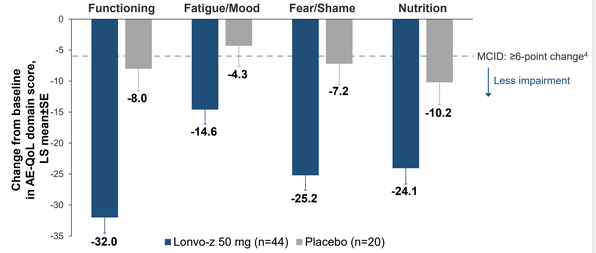
Figure 3. Change from baseline in AE-QoL total score at Week 28



The total score change from baseline at Week 28 was estimated using a mixed model for repeated measures analysis with baseline total score, treatment arm, visit, and treatment-by-visit interaction as fixed effects, and patients as a random effect. For patients who initiated any long-term prophylaxis before the Week 28 assessment, only AE-QoL data collected prior to prophylaxis initiation were included in the analysis. All 16 patients who had not yet reached Week 28 at the time of the data cutoff date owing to later enrollment remained in follow-up, and all available data through their latest assessment were included in the analysis of the AE-QoL total score. No imputation was performed in the analyses.
AE-QoL, Angioedema Quality of Life Questionnaire; LS, least squares; MCID, minimal clinically important difference.

Quality of life meaningfully improved across all AE-QoL domains after a one-time treatment with lonvo-z

Figure 4. Change from baseline in AE-QoL domain scores at Week 28

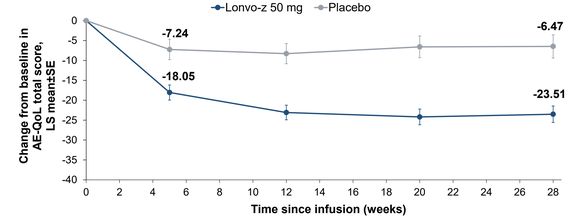


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AE-QoL, Angioedema Quality of Life Questionnaire; LS, least squares; MCID, minimal clinically important difference.

A one-time treatment with lonvo-z 50 mg resulted in a sustained quality of life improvement compared with placebo

- Following lonvo-z 50 mg infusion, AE-QoL total score improved at the first measured timepoint and was significantly improved compared with the total score of the placebo group at Week 28 (P<0.0001; **Figure 5**)

Figure 5. Change from baseline in AE-QoL total score over time



Lonvo-z 50 mg (n)	52	52	52	52	44
Placebo (n)	28	28	27	26	20

AE-QoL, Angioedema Quality of Life Questionnaire; LS, least squares.

Anchor-based thresholds did not meaningfully outperform the established MCID, making the MCID appropriate for the HAELO population

- Anchor-based analysis using the PGI-F-QoL identified an MSD of 10 points using a weighted approach across timepoints (**Table 2**)
- The anchor-based 10-point MSD was consistent with the established 6-point MCID for AE-QoL total score[4] (**Table 3**)
  - The 10-point MSD gave higher specificity and lower sensitivity than the 6-point MCID, but the difference was not large enough to favor either
  - Cohen's kappa coefficient and overall accuracy were consistent across both thresholds
- Additional details are included in the **Supplementary Results**, available by scanning the provided QR code

Table 2. Correlation-weighted MSD estimate for AE-QoL total score

Visit	Mean MSD	r_s	Weight (%)
Week 5 (n=22)	-10.37	0.78	25.3
Week 12 (n=22)	-11.18	0.80	26.5
Week 20 (n=19)	-11.27	0.74	23.0
Week 28 (n=13)	-7.06	0.78	25.3
Weighted MSD[a]	**-9.96**		

[a]Correlation-weighted MSD estimate for AE-QoL total score based on 1-point improvement on PGI-F anchor across 4 timepoints (N=76). Weighted MSD=-9.96 (SE=0.99; 95% CI: -11.91, -8.01). Weights are Fisher's z-transformed absolute correlations per Trigg & Griffiths (2021).[6]
AE-QoL, Angioedema Quality of Life Questionnaire; MSD, meaningful score difference; PGI-F, Patient Global Impression of Frequency; r_s, Spearman coefficient.

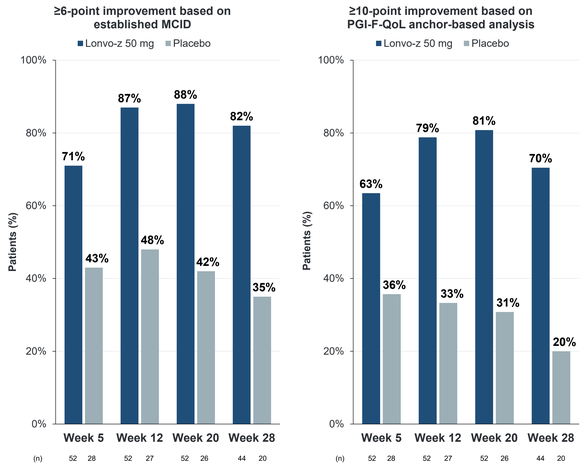
Table 3. Sensitivity and specificity of MSD threshold and MCID at Week 28

	10-point MSD (Week 28)	6-point MCID (Week 28)
Cohen's kappa	0.51	0.52
Overall accuracy	0.77	0.80
Sensitivity	0.72	0.83
Specificity	0.89	0.72

Anchor responders defined as ≥1-point improvement on PGI-F (change ≤-1; n=46/64, 71.9%). Outcome responders defined as AE-QoL improvement ≥ threshold (weighted: n=35/64, 54.7%; 6-point: n=43/64, 67.2%). Kappa interpretation per Landis & Koch (1977)[7]: <0.00=poor, 0.00-0.20=slight, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.80=substantial, ≥0.81=almost perfect.
AE-QoL, Angioedema Quality of Life Questionnaire; MCID, minimal clinically important difference; MSD, meaningful score difference; PGI-F, Patient Global Impression of Frequency.

The majority of patients in the HAELO study achieved a clinically meaningful improvement in AE-QoL total score with either the 6-point MCID or 10-point MSD

Figure 6. Responder analysis for AE-QoL improvement using MCID and MSD (Week 5-28)



AE-QoL, Angioedema Quality of Life Questionnaire; MCID, minimal clinically important difference; MSD, meaningful score difference; PGI-F-QoL, Patient Global Impression of Frequency - Quality of Life.

Conclusions

- In the Phase 3 HAELO study, a one-time treatment with lonvo-z 50 mg demonstrated clinically meaningful and sustained improvements in the total score and all individual domain scores of the AE-QoL compared with placebo
- The majority of the patients treated with lonvo-z 50 mg (70%) achieved a ≥10-point improvement in the AE-QoL total score at Week 28, with a mean improvement of 17.04 points
- Anchor-based analyses identified an MSD of 10 points, similar to the previously established MCID of 6 points, but the slightly better performance of the new threshold did not indicate a need to replace the established MCID, further validating that the AE-QoL and its MCID are appropriate for use in patients with HAE-C1INH
- These disease-specific quality of life improvements, together with an 87% attack rate reduction and favorable safety profile, support that a one-time treatment with lonvo-z can positively impact quality of life and reduce disease burden for people living with HAE-C1INH

This presentation includes data for an investigational product not yet approved by regulatory authorities.

DISCLOSURES:
WRL reports grants, consulting fees, and/or honoraria from AstraZeneca, Astria, BioCryst, BioMarin, CSL Behring, Express Scripts/CVS, Fresenius Kabi, GlaxoSmithKline, Grifols, Intellia Therapeutics, Ionis, KalVista, Magellan, OptiNose, Optum, Pharming, Pharvaris, Sanofi/Regeneron, Takeda/Shire, and Teva; and serves on the board of the US HAEA and the Dallas/Fort Worth Metroplex Allergy Society.

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Supplementary Methods

- PGI-F-QoL is a novel, single-item patient-reported outcome measure that assesses how often HAE affects overall quality of life and was an exploratory endpoint in HAELO
  - Participants answered 1 question using a 4-week recall period: "Over the past four weeks, how often have your swelling episodes (angioedema) had a negative impact on your quality of life?"
    - Responses used a 5-point scale: Never, Rarely, Occasionally, Often, or Very Often
- Cognitive interviews with 16 participants with HAE showed that all interpreted the item as intended; nearly all found it clear, and most interpreted the response options correctly
  - Findings supported using PGI-F-QoL with AE-QoL to capture the impact of HAE on quality of life
- A prespecified, stepwise anchor-based exploratory analysis first evaluated anchor quality. AE-QoL total score changes were then summarized by each 1-category PGI-F-QoL improvement. Timepoint-specific MSDs were estimated from empirical cumulative distribution function curves when change categories showed clear monotonic ordering, distinct distributions versus no change or deterioration, and minimal overlap across the 25th-75th percentiles
- To obtain a single MSD for responder classification, estimates from the 1-category improvement group at Weeks 5, 12, 20, and 28 were combined using correlation-weighted triangulation. Correlation-based weights were estimated between PGI-F-QoL and AE-QoL total score at each timepoint; their weighted average was the final MSD
- Classification performance was assessed using Cohen's kappa (κ), overall accuracy, sensitivity, specificity, and positive and negative predictive values

Supplementary Results: Changes in AE-QoL and PGI-F-QoL were strongly correlated

- Spearman correlations between change from baseline in AE-QoL total score and change from baseline in PGI-F-QoL were strong across all assessed timepoints (r_s=0.74-0.80), exceeding the performance criterion of r_s ≥0.30 (**Table S1**)
  - The stability of the relationship over time, combined with the magnitude of the correlations, supported using the PGI-F-QoL as a suitable anchor for defining clinically meaningful change in AE-QoL total scores in this analysis population

Table S1. Correlation-weighted MSD estimate for AE-QoL total score

Visit	n	Mean MSD	r_s	Weight	Weight (%)
Week 5	22	-10.37	0.78	1.05	25.3
Week 12	22	-11.18	0.80	1.10	26.5
Week 20	19	-11.27	0.74	0.95	23.0
Week 28	13	-7.06	0.78	1.05	25.3
Weighted MSD[a]	**76**	**-9.96**			

[a]Correlation-weighted MSD estimate for AE-QoL total score based on 1-point improvement on PGI-F anchor across 4 timepoints (N=76). Weighted MSD=-9.96 (SE=0.99; 95% CI: -11.91, -8.01). Weights are Fisher's z-transformed absolute correlations per Trigg & Griffiths (2021). SE calculated using Gatz & Smith (1995) analytical approximation.
AE-QoL, Angioedema Quality of Life Questionnaire; MSD, meaningful score difference; PGI-F, Patient Global Impression of Frequency; r_s, Spearman coefficient.

The anchor-based 10-point MSD is consistent with the established 6-point MCID for AE-QoL total score

- Anchor-based analyses identified an MSD of 10 points and evaluated its classification performance versus the 6-point MCID (**Table S2**)
  - Cohen's kappa coefficient and overall accuracy were consistent across both thresholds; the 10-point MSD gives higher specificity and lower sensitivity than the 6-point threshold

Table S2. Sensitivity and specificity of MSD threshold and MCID

	Week 5		Week 12		Week 20		Week 28	
	10-point MSD	6-point MCID	10-point MSD	6-point MCID	10-point MSD	6-point MCID	10-point MSD	6-point MCID
Cohen's kappa	0.56	0.54	0.56	0.56	0.50	0.48	0.51	0.52
Overall accuracy	0.79	0.79	0.81	0.84	0.78	0.79	0.77	0.80
Sensitivity	0.74	0.80	0.79	0.87	0.79	0.86	0.72	0.83
Specificity	0.88	0.77	0.89	0.72	0.76	0.62	0.89	0.72
Positive predictive value	0.93	0.88	0.96	0.91	0.90	0.86	0.94	0.88
Negative predictive value	0.62	0.65	0.55	0.62	0.57	0.62	0.55	0.62

Anchor responders defined as ≥1-point improvement on PGI-F (change ≤-1; n=46/64, 71.9%). Outcome responders defined as AE-QoL improvement ≥ threshold (weighted: n=35/64, 54.7%; 6-point: n=43/64, 67.2%). Kappa interpretation per Landis & Koch (1977): <0.00=poor, 0.00-0.20=slight, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.80=substantial, ≥0.81=almost perfect.
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